Office of Inspector General

Administration Workpaper

Prepared by Chris Dunlap 11/23/2012

Assignment: 2013 - 3540 - OPE-FY13-0001 - Evaluation of EPA's Human Subjects Research
Area: 145
Goal: Sound Science - Improved Understanding of Envionmental Risks - and Greater Innovation to Address Environmental Problems
Type: PERFORMANCE/PROGRAM Subtype: Not Used
Assignment Period: 10/22/2012 through 06/30/2013
Section: C
Assignment Guide Name: Auditee Communication Workpapers

Origination Doclink:
Subject: R1--Entrance Conference **Subsection:** 01

Created by Chris Dunlap on November 26, 2012

Reviewed by: Renee McGhee-Lenart, Nov. 28, 2012, minor changes highlighted in yellow. Workpaper is satisfactory.

Purpose:

To summarize the key points discussed during the entrance conference.

Date of Conference

November 14, 2012

Source:

The sources of the information in this workpaper are the conference participants who are identified throughout this workpaper.

Conference Participants: (the conference participants were in four locations)

Conference Attendees In Washington:

Deborah Heckman, Office of Research and Development (ORD), (202-564-7274)

Robert Kavlock, Deputy Assistant Administrator for Science, ORD (202-564-6620)

Mary Greene, Deputy Director, Office of the Science Advisor, (202-564-7966)

Megan Maguire, ORD, (202-564-6636)

Liz Blackburn, Office of Assistant Administrator (OAA), Immediate Office (IO), ORD, (202-564-2192)

Jim Downing, Executive Director, Human Studies Review Board, Office of the Science Advisor (202-564-2468)

Steve Silverman, Office of General Counsel (OGC) (202-564-5523)

Amy Battaglia, ORD (202-564-6700)

Eric Hanger, Office of Inspector General (OIG) (202-566-0866)

Julie Narimatsu, Program Analyst, OIG, Washington, DC (202-566-2587)

Tempestt Woodard, Program Analyst, OIG (202-566-1364)

Entrance DC Sign-In Sheet.pdf

Conference Attendees In RTP, NC (the location of the meeting was B301 – National Health and Environmental Effects Research Lab (NHEERL),
IO conference room:

Wayne Cascio, Director, Environmental Public Health Division, NHEERL, (919-966-0617)

Dan Costa, OAA, IO, ORD (919-541-2532)

Hal Zenick, Director, NHEERL, ORD (919-541-2201)

Bob Devlin, Senior Scientist, Environmental Public Health Division (EPHD), NHEERL, ORD - Principal Investigator for XCON - (919-966-6255)

David Diaz-Sanchez, Chief, Clinical Research Branch, EPHD, NHEERL, ORD (919-996-0607)

Chris Robbins, Deputy Director, NHEERL, ORD (919-541-2282)

Rick Beusse, Director, Air & Research Issues, OIG (919-541-5747)

Chris Dunlap, Auditor, OIG (919-541-1029)

Entrance RTP Sign-In Sheet.pdf

Video Conference Attendee In Kansas City, KS.:

Renee McGhee-Lenart, Assignment Manager, OIG, KS. (913) 551-7534

Video Conference Attendee In Philadelphia, PA.

Kevin Good, Auditor, OIG, Philadelphia, PA. (215-814-2309)

Scope:

We explained our objectives and discussed the evaluation we have planned to address the Congressional request, including our focus on three human subjects studies (identified as XCON, OMEGACON, and KINGCON) as well as other related studies if they were performed during 2010 or 2011, exposed human subjects to PM-2.5 and/or diesel exhaust, or involved the 41 subjects. We clarified data and information requests and asked and answered questions as appropriate.

Background Information:


Conference Agenda Including Questions.pdf


Entrance Conference Notice.pdf


Notification Memo.pdf

Conclusions:

1. The OIG assignment team needs to contact (b) (6), liaison to the UNC IRB contractor (the assignment guide provides for evaluating the adequacy of UNC IRB's role in the studies; the interview identified (b) (6) as a first contact).

2. None of the 41 subjects who are the focus of our assignment were exposed to diesel exhaust emissions (this statement was made by (b) (6); although OIG representatives will seek to confirm this statement during the evaluation, it is noted that none of the numerous EPA officials attending the conference expressed any reservations about the accuracy of the statement).

3. No other conclusions are drawn in this workpaper. However, the information in this workpaper will be incorporated in other workpaper steps as needed.

Details (Information Obtained):

A. General Discussion:

1. Director Rick Beusse began the conference by discussing the source of the assignment – a congressional request which concerned 41 human subjects that participated in three studies – XCON, OMEGACON, and KINGCON - during 2010 and 2011. Rick explained that generally the OIG would begin an assignment by performing preliminary research. However, since the assignment originated from a congressional request, no preliminary research had been done.

2. Rick further explained that the broad, overall objective of the assignment is to determine whether EPA, as part of its research, followed applicable laws, regulations, policies, procedures, and guidance when it exposed human subjects to diesel exhaust emissions or concentrated airborne particles.

More specifically, the objectives of the assignment are to determine whether EPA, in conducting the XCON, KINGCON, OMEGACON studies, and any related studies exposing 41 human subjects to diesel exhaust emissions or concentrated air particles from 2010 to 2011:

a) Obtained sufficient approval to expose subjects to specific levels of diesel exhaust emissions or concentrated airborne particles;

b) Obtained adequate informed consent from human study subjects before exposing them to diesel exhaust emissions or concentrated airborne particles;

c) Adequately addressed any adverse events that occurred, including:

i) Notifying the University of North Carolina at Chapel Hill's Institutional Review Board (IRB), the Human Studies Review Board, and the Human Subjects Research Review Official of the adverse event;

ii) Revising consent forms as needed, and

iii) Providing clinical follow-up in accordance with the approved protocol.

3. (b) (6) sought confirmation of (b) (6) understanding that (b) (5) [redacted]

4. (b) (6) stated that the phrase "adverse event" is an "IRB designation" – an IRB reportable event. (b) (6) further explained that the terms are used to describe almost any event. If a subject became pregnant, it would be termed an adverse event. (b) (6) asked if we were only interested in an event that put a subject at risk. Rick replied that we were interested in any event that was reported to the IRB as an "adverse event." He noted that this would provide a comprehensive listing of adverse events and that we could use this information to focus on exposed subjects.

5. (b) (6), (b) (5) [redacted]

6. Rick discussed the evaluation process. He said we would be doing preliminary research work at the same time that we would be doing field work. Therefore, we might tweak the objectives during our work. We would advise them if we did that.

7. Rick said during the evaluation process we would be holding their actions up against the criteria. We might also look at their record keeping system. In addition, we would look at other studies in recent times that were related to the objectives of our assignment. (b) (6) asked for Rick's definition of "recent times" and Rick replied that generally, within the last 5 years or so, but explained that we would go back further if we found key information directly on point to our objectives. For example, Rick provided an illustration of a National Academy of Sciences 2002 review of EPA's Human Studies Research that provided advice to EPA on getting informed consent. He said that such key information, even though from 2002, would be within our scope.

8. Continuing to discuss the evaluation process, Rick said we would like to meet with them about once a month. He explained that it would not be precisely every 30 days, but generally about once a month. At this meeting we would share our tentative findings, and seek clarification. Additionally, towards the end of field work we would also share our tentative recommendations with them, once we cleared them through our OIG Counsel. When we got near the end of our field work we would provide them with a written discussion document which would contain everything we intended to put into a discussion draft. We would solicit their comments, including comments on the tone of our write-up, and any additional information they cared to provide. The monthly meetings would be informal, but we would accept written comments from them.

9. Rick said after our field work is completed we would provide them with a draft report. They would have 30 days to respond to this report. We would then meet with them to discuss the draft report and their written comments which might include suggested revisions to our recommendations. Generally, we include their written response as an appendix to our final report. They would have sixty days to respond to the final report. Their response could include actions they have taken or plan to take to address our recommendations.

10. (b) (5) [redacted]

11. (b) (6) [redacted] asked if they would see the final report before it was public. Rick replied that yes, both EPA and the Hill would get the final report one day before we put the report on the OIG web site.

(b) (6), (b) (5) [redacted]

Rick cited the specific section of the IG Act (Section 6) that authorized OIG representatives to see everything that the agency representatives see.

> **[Evaluator's Note: Section 6 of the IG Act states that:** (a) In addition to the authority otherwise provided by this Act, each Inspector General, in carrying out the provisions of this Act, is authorized: (1) to have access to all records, reports, audits, reviews, documents, papers, recommendations, or other material available to the applicable establishment which relate to

programs and operations with respect to which that Inspector General has responsibilities under this Act; . . ."]

Rick said the OIG's authority is clear in the Act and clear on his credentials. To emphasize his point, he read the following excerpt from his credentials: "pursuant to the Inspector General Act of 1978 as amended . . ." we are authorized to "have unrestricted access to all EPA records, information, and facilities . . ." Rick said being denied access would be a significant obstacle to our being able to do our work (b) (5) [redacted]. Rick made the point that the fact that we see the information does not mean we will report it outside of the Agency. However, in order for us to get started reviewing the consent forms immediately, Rick said we recognized that in the interim until our Counsel meets with OGC that we could code the information, at least in the short run. A code number could be used in the short run in place of a subject's name, but we also need to link the code to a specific date and time that a subject was exposed. We could work with the specific information for specific coded names in the interim.

(b) (6), (b) (5) [redacted]

(b) (6) [redacted] said the UNC IRB is a contractor. They would have concern about disclosing PII. They would not want any PII to be copied or leave their premises, but they might allow us to look at the information.

(b) (6), (b) (5) [redacted]

(b) (6) [redacted] said [redacted] did not think the IRB would be OK with OIG contacting the subjects.

(b) (6) [redacted] said [redacted] concern was there was nothing on the consent form where the subject says you have my permission to release information about me. [redacted] further said that Section 112 of the Clean Air Act requires that this type of information be secured.

(b) (6), (b) (5) [redacted]

B. OIG Written Questions And ORD Responses To These Questions Which Were Provided In Advance

1. OIG Question:

Which EPA offices and laboratories conduct human exposure studies; i.e., studies where EPA or its contractors exposes human subjects to pollution? Besides air pollution, what other media are studied this way?

ORD Response:

(b) (6) said that NHEERL was the only EPA office that exposed human subjects to pollution; it is the only office that has the capability of exposing human subjects to pollution. [Auditor's Note: OIG conclusion is that these are intentional exposures since intentional studies are being done.] However, EPA also provides funding in which universities and other labs expose human subjects to pollution and EPA also reviews studies by other entities that expose human subjects to pollution. Similar studies are done worldwide which expose human subjects to the same pollutants that were used in the three studies that are the focus of OIG's review. Almost all of NHEERL's human health studies involve air pollutants; (b) (6) said could only remember one study that did not involve air pollutants in the last 20 years and that involved dermal exposure.

In regard to OIG's follow-up question above about what other media are studied in this way, (b) (6) said pharmaceutical companies support numerous human health studies related to the drugs they hope to market and other companies support human health studies concerning fragrances.

2. OIG Question:

Please describe the organizational structure, roles, and responsibilities of the Office of the Science Advisor as it relates to approving or overseeing human exposure studies? In particular:

a. What is the role of the HSRB?
b. What is the role of the HSRRO?

ORD Response:

(b) (6) stated that the HSRRO approves all studies that expose human subjects to pollutants. Any time a revision is made in a proposed study, the HSRRO must approve the revised study protocol.

(b) (6) said that the HSRB focuses on third-party studies involving pesticides. The HSRB is a FACA (a Federal Advisory Committee Act committee). All studies that go through the HSRB have already been approved by the IRB. The HSRB provides input back to the pesticide community. It is not involved with EPA's studies that expose humans to air pollution. It serves in an advisory role; it does not approve EPA human subject studies.

(b) (6) said that the Office of the Science Advisor (OSA) has a record system to track all projects. The record system was improved in 2007, so it is more robust from 2007 on. OSA also provides training, education and broad oversight in human subject research. Rick asked about OSA's training. (b) (6) said that Human Research Protocol Officer's (HRPO's) purpose is education and training. (b) (6) further stated that the (b) (6) had detailed training modules when went out. worked with labs that also had online training. (b) (6) said would provide us with the links to the training.

Rick asked whether training materials were online. (b) (6) responded that everyone has to undergo CITI training - it's an IRB requirement. CITI training is from the National

Institutes of Health.

(b) (6), (b) (5) [redacted]

Julie asked whether the HSRRO is under the Science Advisor or is organizationally adjacent to the Science Advisor? (b) (6) responded that the HSRRO is under the Science Advisor.

Renee asked about the role of the HRPO. (b) (6) said that HRPO is within EPHD and that they were in the process of filling this position. (b) (6) [redacted]

3. OIG Question:

Please describe the organizational structure, roles, and responsibilities of NHEERL as it relates to approving or overseeing human exposure studies?

a. Which divisions of ORD's National Health and Environmental Effects Research Laboratory are involved with the direct exposure of human subjects? What are their roles?

b. Which branches of the Environmental Public Health Division are involved with the direct exposure of human subjects? What are their roles?

ORD Response:

All of EPA's human exposure research is done in the clinical research program.[Auditor's Note: The formal name of the branch is Clinical Studies Branch in the Environmental Public Health Division.] As noted previously, NHEERL also looks at exposure studies that were completed by entities that are not affiliated with EPA.

(b) (6) said that all the reviews within NHEERL and HRPO are in Appendix A of the materials given to the IG - there's a summary of all the people involved. There are two additional reviews – one by the EPA dosing review officer and one by the EPA quality assurance officer. However, at the moment there is only one EPA person who is filling both roles. The HRPO ensures that any human research proposal meets the requirements of the Common Rule. A physician reviews the safety of the protocol. After the HRPO has approved a proposal it goes to the HRPO Director for approval and (b) (6) [redacted] and then to the Associate Director of Health for approval. Then to the HSRRO.

(b) (6) said that the external reviews are required by EPA, but not the IRB. (b) (6) also said that the IRB package also has to have a study justification document that outlines the benefits and risks.

Renee asked would the dosing officer be involved with the three "CON" studies. (b) (6) answered that "it depends." (b) (5), (b) (6) [redacted]

(b) (6) [redacted] is the liaison with the contractor. Renee said we will need to talk with (b) (6) [redacted]

(b) (6) said that they would also provide the contact information for the Dosing and QA officer.

(b) (6), (b) (5) [redacted]

4. OIG Question:

What is the statutory basis for human research studies?

ORD Response:

(b) (6) said that Section 103 of the Clean Air Act (CAA) is the statutory basis for human research studies. This Section mandates that EPA conduct human and animal study research. This information is in the thumb drive they provided to OIG.

5. OIG Question:

What laws, regulations, policies, procedures, guidance, and protocols does EPA use to guide its human subject research?

a. 40 CFR 26

b. EPA Order 1000.17 Change A1.

c. NHREEL Guidance

d. University of North Carolina IRB Guidance

e. Additional laws, regulations, policies, procedures, guidance, and protocols?

ORD Response:

(b) (6) said (b) (6) doesn't know of any additional guidance.

(b) (6) said they are guided by other documents and have included them in the materials provided to the IG. There was a 2001 paper which predates the NHEERL guidance and that some of the language was taken directly from that document.

6. OIG Question:

Our scope includes the KINGCON, OMEGACON, and XCON and any related studies exposing 41 human subjects to concentrated air particles or diesel exhaust emissions from 2010 to 2011. Besides KINGCON, OMEGACON, and XCON, are there any other related studies that meet those criteria? Please identify.

ORD Response:

(b) (6), (b) (5)

(b) (6), (b) (5)

(b) (6) stated there were two diesel studies. One study was called "LAMARK." There were approximately 30 human subjects in this study which concerned molecular changes in airways from exposure to ozone and other pollutants. The effects of the exposure were minimal. The other study (designated by the acronym DEPOZ) concerned ozone and the synergistic effects of concentrations of multiple air pollutants. There were also approximately 30 human subjects and this study did not lead to any major findings. There were only about 15-20 participants during the 2010-2011 timeframe and, additionally, not all participants were exposed. Some dropped out or we couldn't schedule them or we decided they were not appropriate. No information about these two diesel studies was included in the thumb drive that was provided to Auditor Dunlap. We can provide information if needed.

7. OIG Question:

Please briefly explain the approval process for the specific studies we are reviewing. Is the

HSRB involved in the approval process of any of the studies?

ORD Response:

(b) (6) said discussions will take place concerning health effects of multiple pollutants. A Principal Investigator (PI) will design a study to address an issue and draft a protocol. This protocol is sent to the EPA/ORD/NHEERL/EPHD Clinical Research Branch Chief. If the Branch Chief approves it, the protocol goes to the medical staff. After the medical staff approves the protocol it is sent to the IRB and two outside sources who look at the ethical, scientific and safety issues.

The proposal then goes to the Quality Assurance Officer (QA sees it before the IRB but doesn't sign off at that point), then there's a statistical review unless there's a statistician on the protocol. Then the Dosing Officer. After approval is obtained, the proposal goes to the HRPO (HRPO has also seen it before the IRB but doesn't sign off at that point). Then a complete package is assembled (including such items as a fact sheet and study justification document).

Then the proposal goes to the Associate Director of Health, then to the HSRRO for approval (see workpaper B-07c). After all of these approvals have been obtained there is a meeting where all of the concerned parties, including the contractors and the quality assurance officer, discuss the study. At this point in time, all roles during the study are clearly defined and assigned.

(b) (6) said that IRB's approval is only good for one year. After each year of a study, all of the information is reviewed by the IRB and the approval must be provided again, for the next year. If the protocol receives any modification at any time, if one name is added to the protocol, it goes back to the IRB for a new approval.

(b) (6) clarified that the annual review usually doesn't go to the full IRB. The IRB has an option for expedited review.

8. OIG Question:

How does EPA decide to use human research exposure studies to satisfy its goals rather than other types of studies?

ORD Response:

(b) (6), (b) (5)

(b) (6) said there is a paper trail concerning the development of research study proposals but since we did not ask for this paper trail, it was not provided in the thumb drive that was

given to OIG.

9. OIG Question:

How does EPA plan to use the information from the XCON, OMEGACON, KINGCON, and any related studies?

ORD Response:

(b) (6), (b) (5)

(b) (6) said the XCON study addressed the question of whether human bodies are responsive to increases in certain air pollutants. Forty two million people have risk factors. Are these people more responsive; are they more at risk from air pollutants. "Responses" are different than "adverse effects." Responses are not of clinical significance but they tell us about the mechanisms.

(b) (6), (b) (5)

(b) (6) said OMEGACON was designed to answer the question whether fish oil (omega 3 fatty acid supplementation) might produce a human response when air pollutants were breathed. The question behind the study was, given that many people are living in nonattainment areas, are there things that people can do to help cope with the air pollutants?

(b) (6) said the KINGCON study also addressed the question of whether human bodies are responsive to increases in certain air pollutants.

10. OIG Question:

How did EPA determine the risk level of the individuals being exposed to the concentrated air particles/diesel exhaust? What was the level of risk?

ORD Response:

This question was address in ORD's response to the next question.

11. OIG Question:

How were the human subjects informed about the level of risk?

ORD Response:

(b) (6) said the risk is communicated orally and in the consent form. When a potential subject expresses interest in being part of a study they are asked to complete a screening questionnaire. There are "exclusion factors."For example, if they are a smoker they are excluded. Then EPA staff will explain the protocol to potential subjects and they will be shown the consent form. The first screening usually takes place over the telephone.

After the initial screening the subject will be interviewed at HSD facility on the campus of UNC. The PI will show the potential subjects the consent form and the PI will go over every section of the form and ask do they understand. All pertinent aspects of the study will be discussed with the potential subject including (a) the reason for the study, (b) the type of air pollutant to which the subject will be exposed, (c) the risks and benefits to the subject and society, and (d) the people that can be contacted if the subject has questions or problems during the study, including the phone number of a physician associated with the study. (b) (6) said the benefits to the subject are usually low, usually just fiscal and the value of the physical they receive, but that's typical of these studies. Different PIs go over the consent form with the subject in different ways – some will ask the potential subject to repeat the information, some will simply ask do you understand. The potential subject is always asked does he/she have any questions.

Rick asked whether there is any documentation or recordings of the oral presentations made to subjects. (b) (6) responded that they have documents with PI's describing what they do, but no recordings. (b) (6) added that they have a system of training new PIs. (b) (6), (b) [redacted]

Rick asked whether there was a training certification program for PIs. (b) (6) responded that there was no formal training, but new investigators have to be under the guidance of an experienced PI and that they will not become a PI until the HRPO, Branch Chief and PI think they are capable.

(b) (6) said the Protocol Officer and others try to make the information that is provided to the potential subjects as easy to understand as possible. The goal is to write the information at the 6th or 8th grade level. The IRB and others make sure the forms are understandable.

After being provided with the information, the subjects are asked to go away, think about the information, and come back the next day.

(b) (6) said during the study, the subject stays in the medical facility. They are observed,

their blood samples are taken on the day of exposure and the next day. We follow up on them. (b) (6) added that a physician is in the building at all times during the study.

Rick asked do the subjects get a physical. (b) (6) answered affirmatively. Blood will be drawn, chemical markers will be checked, etc. (b) (6) said that in most cases the subject are not exposed to pollutants on the same day that the Agency obtained their informed consent; in most case the subjects will be asked to come back the next day. (b) (6) summarized that there will always be (a) a screening questionnaire, (b) interview, (c) physical, and (d) lab test.

(b) (6), (b) (5)

Rick asked whether there had been any complaints from subjects. (b) (6) responded that there hadn't been in the (b) (6) has been there. (b) (6) said there had actually been letters thanking them for the treatment they were given. (b) (6) added that they see a lot of repeat subjects and they had to put rules on participation frequency. (b) (6) suggested that we talk to the nurses.

12. OIG Question:

How many adverse or unexpected events or unanticipated problems that occurred during 2010 and 2011 involved human subjects exposed to concentrated air particles or diesel exhaust? Please describe what occurred.

ORD Response:

(b) (6) said we need to understand that an "adverse event" is almost any event. If a subject gets pregnant during the study this event is an adverse event because the subject can no longer participate in the study. If a subject faints while blood is being drawn, this event is an adverse event. They have come up with a new term – a "serious adverse event." They have never experienced a "serious adverse event." In some cases a subject's heart rate has gone up, but they expect that to happen; that is not a "serious adverse event."

(b) (6) said there have been four "adverse events" and they prepared one letter to explain why no "adverse event" report was submitted in the case of a fifth event where the subject was referred to a doctor (the event was anticipated and was not linked to the study). One of the events was a migraine (b) (5) They changed recruiting so that people with a history of migraines were excluded. Two of the other four events were an increase in the heart rate which were expected events.

(b) (6) described the fourth event - a (b) (6) subject experienced atrial fibrillation (a change in the normal rhythm in the upper chamber of the heart). The

abnormal rhythm was identified because they had excellent monitoring equipment (a wireless telemetry system). If the abnormal rhythm continued for several days without treatment there would be a risk of a heart attack or a stroke. While waiting to go to the hospital, the abnormal rhythm disappeared. The event was reported as an "unanticipated problem." The IRB said there was no reason to change the protocol. It was learned subsequently that [redacted] probably had been having abnormal heart rhythms all along but did not know it. There was no evidence of a periodic abnormal heart rhythm in an EPA human subjects study [redacted] participated in [redacted] earlier. They concluded that the exposure was a trigger, but [redacted] heart was predisposed to go into the abnormal rhythm. [redacted] subsequently had treatment for [redacted] condition and steps were taken to prevent the abnormal rhythm from reoccurring. [redacted] told them that they saved [redacted] life.

[redacted] said the exposure did not create any risk or add to any risk. The [redacted] risk of a stroke or heart attack was the same after the exposure as it was before the study.

Rick asked have there been any complaints from any subjects after the studies. [redacted] replied that there had not been any in [redacted] years [redacted] has been here.

[redacted] said that the subjects are very happy to be part of the studies. They are altruistic. They feel like they are part of something special; they feel like they are contributing to something positive. They talk with the nurses.

13. OIG Question:

Please describe any changes to the tests as a result of adverse or unexpected events.

ORD Response:

No additional information was obtained. The conference had lasted its scheduled length. Another conference was scheduled to begin and the participants in the pending conference were standing outside the conference room. [redacted] said [redacted] thought they had already provided the information needed to answer this question.

14. OIG Question:

Please describe any changes to the process of getting informed consent for the subjects as a result of adverse or unexpected events.

ORD Response:

[redacted] added just the migraine example where they excluded people with a history of migraines. Otherwise, for the atrial fibrillation event, they have not changed the process because neither EPA nor the IRB saw the need to change the process.

15. OIG Question:

We will be requesting information from ORD and OSA that will include the files given to the IRB and HSRRO for review as well as consent forms. Will any of the study subjects' medical information (PII) be in those files? If so, will we receive copies of this information or will certain information be in the Medical and Research Study Records of Human Volunteers database? How quickly can we receive this information?

ORD Response:

(b) (6) said there is not PII information in the files we received (via the thumb drive discussed earlier). (b) (6) said the only information [redacted] receives about subjects is general information such as (a) the subject is over 50 years old and (b) has mild asthma.

I have reviewed the above w/p and found it satisfactory. - 05/15/13 (Note: w/p write-up reviewed in MS Word and comments provided via e-mail on 11/19/12.).

Status: Approved		**Send To:**	
Current Editor List:			
Level 1 approval:	Approved	Renee McGhee-Lenart	04/03/2014 10:02:51 AM
Level 2 approval:	Approved	Rick Beusse	04/03/2014 03:27:02 PM

Linkage Information

History

Office of Inspector General

Administration Workpaper

Prepared by Kevin Good 05/22/2013

Assignment: 2013 - 3540 - OPE-FY13-0001 - Evaluation of EPA's Human Subjects Research
Area: 145
Goal: Sound Science - Improved Understanding of Envionmental Risks - and Greater Innovation to Address Environmental Problems
Type: PERFORMANCE/PROGRAM Subtype: Not Used
Assignment Period: 10/22/2012 through 06/30/2013
Section: C
Assignment Guide Name: Auditee Communication Workpapers

Origination Doclink:
Subject: R1-ROC of NHEERL interview - (b) (6) Subsection: 06

Name	Date	Acti
Tempestt Woodard & Kevin Good	May 28, 2013	Created WP
Renee McGhee-Lenart	May 30, 2013	Reviewed workpaper. Minor c satisfactory.
Julie Narimatsu	July 25, 2013	Edited workpaper to add Source 7 a
Renee McGhee-Lenart	August 5, 2013	Reviewed workpaper and found it to

Purpose: To ask follow-up questions of (b) (6) .

Source:
May 15, 2013 at 10 am ET

Attendee's Name	Office/Title	Phone
(b) (6)	(b) (6)	(b) (6)
(b) (6)	(b) (6)	(b) (6)
Renee McGhee-Lenart	EPA-OIG Assignment Manager	913-551-7534

Chris Dunlap	**EPA-OIG Auditor**	**919-541-1029**
Kevin Good	**EPA-OIG Auditor**	**215-814-2309**
Alicia Mariscal	**EPA-OIG Social Scientist**	**202-566-1858**
Julie Narimatsu	**EPA-OIG Program Analyst**	**202-566-2587**
Tempestt Woodard	**EPA-OIG Health Scientist**	**202-566-1364**

Source 1 (Attachment-1) List of Questions

Interview Questions for (b) (6) _05_14_13 (2).docx

Provided Documents
Study Abstracts -
Source 2:

xcon abstract 2009_ATS.DOC

Source 3:

ATS2012 abstract_cbsV2.docx

Source 4:

Circulation-2012-Devlin-CIRCULATIONAHA.112.094359.pdf

Source 5:

Omega-3 Supplementation attenuate PM-induced cardiac effects & lipid changes in middle-aged - 7-2012a.pdf

Source 6:

Follinsbee 1980.pdf

Source 7:

July 24 Email.pdf

Scope: Followup meeting to discuss questions about consents forms, adverse events, EPA's approval process, and a few other topics.

Conclusion:

No conclusions were made based upon this interview.

Results:

RML: We're finalizing our field work right now as well as starting preliminary report writing. We're still scheduling human subject interviews. We had five interviews two weeks ago and are still having trouble getting a few lined up. I spoke with Rick and in June we agreed to meet you to discuss our findings.

I know these questions are things we've discussed before, I apologize in advance, but we want to make sure we understand the issues.

(b) (6) We understand and appreciate you sorting through the volume of information, and you can ask as many times as possible, we want to help you understand.

Study Results

1. **Have any articles/results been published based upon the 5 studies (KINGCON, XCON, OMEGACON, DEPOZ, or LAMARCK) we have reviewed? (We have a copy of the journal article published about the XCON subject with atrial fibrillation.)**

(b) (6) For KINGCON, (b) (6), (b) (5) [redacted]. XCON –

(b) (6), (b) (5) [redacted]. There is an abstract that's been presented in a meeting.

(b) (6) [redacted] Would you like to have a copy of the abstract? (See Sources 2 and 3)

RML: Yes, we would appreciate a copy of the abstract.

(b) (6) [redacted] (b) (5) [redacted] .(See Source 5)

(b) (6) [redacted] (b) (5) [redacted]

(b) (6) [redacted] We can send you the abstract. (See Source 4)

(b) (6) [redacted] (b) (6) [redacted] is writing up the paper. (b) (5) [redacted].

IRB Procedures

2. **According to 40 CFR 26, EPA must include written procedures for the IRB to follow during its reviews as well as procedures for ensuring that unanticipated problems involving risks to subjects are reported to the IRB and other officials. What procedures has EPA developed for the IRB to follow?**

(b) (6) [redacted] (b) (5) [redacted] The UNC IRB has those procedures in the

form of Statement of Procedures (SOP). (b) (5) [redacted]

Follow-up 1 - RML: UNC SOPs?

(b) (6) UNC has an SOP doc that I believe you have access to?

RML: Yes, we have copies.

(b) (6) My interpretation is (b) (6), (b) (5) [redacted].

(b) (6) (b) (6), (b) (5) [redacted]

Approval Process

3. **For KINGCON, we do not have the approval letter from the NHEERL Associate Director for Health (ADH). We have a letter from the NHEERL Associate Director to the HSRRO stating the study is ready for (b) (6) review, and that (b) (6) believes the study proposal complies with the Common Rule. (b) (6) stated that this is the only letter (b) (6) has from the Associate Director. Should there be a separate approval memo from the NHEERL Associate Director? If so, can someone check the records to see if one exists and provide us with a copy?**

(b) (6) For KINGCON, it's a modification. So it needs to go to HSRRO for approval. It doesn't have to have all the sign offs on the sign off

sheet. We do that quite often, which leads us to #4. The key here is that the ADH states it complies with the Common Rule. The key is that the HSRRO reviews it. There is no formal requirement that there be a separate approval memo.

4. **What is the approval process for study modifications? Does EPA have policies, procedures, or guidance concerning this issue?**

We follow NHEERL Guidance document. If there is a major modification which significantly alters risk, it will be given to the HSRRO. The question becomes what is a major modification that modifies risk. That's not explicitly stated out there, because it depends on the context, and that decision resides with the HRPO.

Follow-up 2 - RML: What happens when that position isn't filled, who makes the call?

(b) (6) We recognize that not having a HRPO in place is a potential vulnerability and that' why we strive to fill it. To my knowledge there hasn't been a modification apart from telephone numbers and administrative procedures. The Branch Chief and the DD would decide whether or not a modification was significant in the absence of the HRPO. We have contracted out the functions of that position, (b) (5) [redacted].

Follow-up 3 - RML: Currently, who is serving in that role, or is it a variety of people at the moment?

(b) (6) [redacted]

(b) (6) Now remember this is a personal service contract position. (b) (5) [redacted]

Follow-up 4 - RML: How long is the contract for?

(b) (6) The contract is for a year, but we will extend it if needed -- (b) (5) [redacted]

Follow-up 5 - RML: Will (b) (6) be moving to D.C. or will (b) (6) stay in (b) (6)

(b) (6): (b) (6) will stay in (b) (6) (b) (6) will be doing this on (b) (6) own time as part of the contract. One of the issues with that is we had to cap the number of studies (b) (6) had to review, because this isn't (b) (6) full-time job. Part of HRPO's job is to review and interface with IRB, log protocols and any calls etc., answer and fielding questions. The HRPO, (b) (6), won't be doing that. The administrative portion of the HRPO functions will be done by (b) (6). (b) (6) will not be making decisions or reviews. (b) (6) doing the more laborious and administrative portions of the work.

Follow-up 5 - KG: Did you have to determine whether the HRPO is inherently governmental?

(b) (6) Yes, it was determined that it was not inherently governmental, because the HRPO is not giving approval. They are just providing a recommendation to the division director whether the protocol can proceed. The only person who can approve a protocol is the HSRRO. Even (b) (6) signature means that they agree and it can move forward.

Follow-up 6 - RML: So are you saying it comes down to the IRB and HSRRO?

(b) (6) Technically, it's semantics. The only person to grant approval is

the HSRRO. It doesn't get to the HSRRO's desk if everyone below it does not agree or approve. Everyone has veto power, but no one can grant approval.

RML: It's technical, but important to us. One of our objectives asks if the proper approval was granted, so I wanted to hear your explanation.

(b) (6) The HRPO gives approval for the protocol to continue to the next step in the chain, but not for the study start.

5. How do you ensure the independence of extramural reviewers?

(b) (6) External reviewers are conducting the review voluntarily, and are experts in field with experience. There are no monetary incentives for favoring EPA studies. They're not approving it in any way; only making recommendations based on quality, integrity, and safety of subjects.

(b) (6) If the question is – is there a possibility for EPA funding from another source? There is a possibility, but it doesn't influence their independence. Everyone who goes to National Institute of Health (NIH) panel is NIH funded, but they don't get funding from us.

RML: I know in EPA's peer review handbook it discusses the difference between "peer review" and "peer input", and a key difference being the level of involvement and indepence. If they don't have these things, we have to determine whether there is an internal control weakness.

(b) (6) Selection of reviewers is something that typically comes from the Branch Chief. The Branch Chief has to justify why the individuals were picked. (b) (5) We have to justify that they are Subject Matter Experts and have the required experience. It's almost inevitable that we know them. This is peer input. It's not a formal peer review. We're not paying them. The way to view this is like a journal. We send papers to the

journals and they send to two independent reviewers, and the editor decides whether to publish it.

Follow-up 7 - RML: Do you feel there's a place for adding a peer review process into your structure?

(b) (6) Again, if you look at some place like the NIH or our collaboration at UNC or at any establishment in the world, they don't go through that step. (b) (5) [redacted]

Follow-up 8 - KG: I just wanted to clarify the peer input comment. According to EPA's definition of peer input, the reviewer would have to have considerable involvement in the development of the protocol.

(b) (6) That being the case then I misspoke. (b) (5) [redacted] My comment was only to mean that there are reviews that are just reviews and are not formal approvals.

CD: I'm concerned about independence, and I understand that you will know the peer reviewers.

(b) (6) If it can be improved it would be a good recommendation for us to update the guidance document.

(b) (6) What is meant by independence, but I'm more that amenable to improve the process.

6. **Who served as the Division Human Research Officer during**

the last 5 years? If that position has been vacant for a while, who conducted that position's review and approval of protocols?

(b) (6), (b) (5)

[redacted]

[AM Analyst Note: While (b) (6) says that no one has ever signed that line (of the NHEERL sign-off sheet), for KingCon, see WP 18.2, Source 3, p. 5 for (b) (6) signature (the HRPO Director at the time) on the DHRO signature line and XCON, (b) (6) signed off as HRPO and Division Human Research Officer(F-18.1, SOURCE 1, page 6).]

Risk

7. **Question for** (b) (6) . (b) (5)

[redacted]

(b) (6) (b) (5)

[redacted]

(b) (5) [redacted]

[redacted]

Follow-up 9 - KG: Even with physical exam initially before study starts, you don't really know how healthy they are because there's still a risk for unknown conditions. Just tailoring risks to them is that adequate?

(b) (6) It's not that we don't tell them the risk to society or the individuals. It's what you emphasize.

(b) (6) It's about understanding the health of the individual. The medical screening is pretty extensive. It involves a physical exam; lab tests; and a detailed medical history and questionnaire. The questionnaire asks for greater detail depending on whether we want to understand risks or uncover health issues the individual may not know about. We recommend they see a physician when we find things they didn't know they had, if they go through screening with no abnormalities and have a risk probability of a low or intermediate. Risk for a 10-year risk of a cardiac event we feel their risk from exposure to ozone, PM, and diesel is very low.

Follow-up 10 - KG: Even with these procedures in place, there were individuals who were found to have previous conditions. But we might be able to go into further detail when we ask question 17.

Consent Forms/Pollutant Exposure

8. **Is there a reason why only one study's consent form identifies the potential exposure level range to the study participants? (Note: XCON2 mentioned an upper range of pollutant exposure as 600,000 particles per cc.) Has your division considered putting in the pollutant standards (if they exist) into the consent forms?**

(b) (6) There are three aspects to that. 1) First, the studies have different authors. Different scientists write in different styles. 2) It's a technicality, before we were not able to get high particle counts. There was no upper boundary in XCON1.

Follow-up 11 - RML: We are not just comparing XCON – we are looking at the other studies too.

(b) (6) (b) (6), (b) (5)

[redacted]

(ANALYST NOTE: In a follow-up email on 7/24/13, (b) (6) **stated: "**(b) (5)

[redacted]

(b) (5) [redacted]

(b) (6) [redacted] working on standardizing the language about risks of the
pollutants in consent forms. Can you clarify how this will be standardized, e.g. will it be put in NHEERL procedures?
Thank you,
Julie

Follow-up 12 - RML: We noticed that too and in the others it's not. XCON mentions an upper range of exposure. In some cases, they may not have known that, but we wanted to clarity as well.

(b) (6) It is not relevant. The PM NAAQS standards are based on annual standards over in an area which can be exceeded. Consent forms have to be written at a 6-8th grade education level; they need to be understandable. It's not relevant to that exposure. I think we would get a lot of push back from the IRB if we used micrograms per cubic meter.

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9. **Why didn't the LAMARCK and DEPOZ consent forms state that exposure to diesel exhaust may cause cancer? Should consent forms address only short-term risks?**

DDS: The risk is exceedingly low. Those risks are based on chronic, long term, occupational levels which are extrapolated to the environment. They all talk about chronic exposure. It's important to understand the difference between an acute exposure and short term, long term risk. All that we do are acute and short term, and do not have a long term risk. (b) (6) has a good example.

(b) (6) You can have studies that have long-term risks without any

short-term risks. For example, a clinical cardiovascular study where the protocol requires a chest CT scan. The individual agrees and receives a fairly large radiation dose. There is no short-term risk from that procedure, but there is a calculable long-term risk of developing lung cancer or breast cancer in women. There has to be a statement in the consent form of that. We don't have long-term risks of the human studies we do.

(b) (6), (b) (5)

[redacted]

[redacted]

[redacted]

.

Follow-up 14 - KG: Do you think that (b) (5)

[redacted]

(b) (6), (b) (5)

[redacted]

[redacted]

(b) (6), (b) (5) [redacted]

[redacted]

Follow-up 15 - RML: Can you tell us where to find the risk calculation that diesel exhaust causes cancer?

(b) (6) I'm pretty sure you have them. At this case you probably have 10,000 pgs. It may be easier for us to just send it to you.

(Reviewer's Note: We had the calculations in an attachment to the (b) (6) [redacted] interview, see WP F.16.g, see documents provided, see (b) (6) Estimates Cancer Risk attachment)

10. **Is there a reason why XCON and DEPOZ consent forms mentioned the risk that older people with cardiovascular problems could lead to death while the other studies did not?**

(b) (6) It was written by different individuals. In XCON the age range is slightly higher. We're working on standardizing the language so there's none of these inconsistencies.

11. **Is the risk of death a "reasonable" and "foreseeable" risk in the five studies we are reviewing (the words reasonable" and "foreseeable" are contained in the CFR)?**

(b) (6) No, it is not reasonable or foreseeable, which leads us to question 12.

12. **What is the basis for the following statement:**

"Exposure to the air pollution particle concentrations

used in this study for short periods of time has never been found to cause permanent health effects."

Is there an authoritative article or study that reaches this conclusion? What statistics exist to support this statement? No. there's no authoritative study that taking blood from individuals. causes death. People don't publish those types of studies. Or PFT causing cancer. We came to that conclusion b/c these are healthy individuals. And the mechanisms don't seem to be appropriate. It's not in the literature and has never been a reported case.

(b) (6) There are no mechanisms that we understand that would happen in these healthy individuals. There's no track record.

(b) (6) There's over 100 CAP studies and 20 people per study. This is a small research community. If there was a serious adverse event or adverse event we would know about it. (b) (5) [redacted]

Follow-up 16 - RML: Is that why you don't have much to report to IRB?

(b) (6) Yes, that's true. The risk for air pollution is really quite small, but the reason it is a public health problem is because the problem is over 300 million people.

(b) (6) Between the years of 2010-12, Harvard University published a paper that updates the effects of air pollution over a cardiovascular system. No consistent data that individuals greater than ages 65-75 are at an increased risk to effects of air pollution. They cannot find a risk in healthy individuals.

13. **In one of our interviews, we were told that breathing 420 µg/m^3 for 2 hours is the same as 35 µg/m^3 for 24 hours. Can we receive a copy of the research that concludes this?**

(b) (6) I can write it on a napkin. It's a mathematical calculation.

Follow-up 17 - RML: So it's straight-line math?

(b) (6) It's a relative value. If you really wanted to know what dose an individual would get, you have to do a calculation of concentration in the air volume breathed over a 24 hr period. That would give you a dose. Particles come in on inspiration and come out on expiration. This calculation gives you a sense of a 24 hr to 2 hr exposures.

14. **Please discuss the basis for the smoggy day statements (e.g. ". . . the amount of particles you will be exposed to is less than what you would likely encounter over 24 hours on a smoggy day in an urban area."). What evidence supports this statement?**

(b) (6) It's a simple calculation of what a level is in a smoggy city over 24 hrs.

Follow-up 18 - Is the smoggy day statement sufficient to convey the "reasonable" and "foreseeable" health risks of being exposed to the pollutants in the five studies we reviewed (this question is not concerned with the risk of medical procedures)?

(b) (6) That's not the purpose of that statement or #13 either. Those are not there to provide information about risk to the individuals. They are there to provide a context in laymen's terms. If we say you're breathing 420 micrograms per cubic meter, they have no idea what that means. It's to give a context of what exposure it is similar to. The risk that

(b) (6) said is dependent on the individual and individual's health, which is more of the driving factor in the dose.

(b) (6) Just this morning, I went on the internet and AQI in San Bernardino, CA which equates to $PM_{2.5}$ at 40 ug/m^3 which is equivalent to our exposure at 475. We don't even state "like level of Bejing" anymore, because our state department people were exposed to levels in excess of 800 ug/m^3 overseas.

Adverse Events

15. **According to the IRB electronic document, even if an adverse event is not reportable, EPA still may have obligations to report an adverse event to the research sponsor, coordinating center, data safety monitoring board, or other oversight committee. Does EPA report adverse events to any other entity?**

(b) (6) #15 is asking whether we have a DSMB or some type of reporting entity. The HRPO acts as a DSMB. The HRPO collects all the adverse events and sees if there is any trends or areas to be aware of. The answer is yes we report to the HRPO.

16. **What is the definition of "clinically significant" symptom levels that would cause, for example, the DEPOZ PI to stop the study completely (and not just for one or more exposure sessions) for a given subject?**

(b) (6) "Clinically significant", we would determine it to be an adverse event according to the guidelines. Historically, we did not have a formal guideline for the number of adverse events that would stop a study. The HRPO would monitor that and make consultation. However, now when we do IRB submissions there are questions and they are: what are the criteria used to withdraw people from study. Then 2nd question is: are their criteria to stop the entire study (inability to recruit, for example), and we have to explain what criteria will be used to stop the study? We

now include defined stop criteria in our submissions not for the individuals, but also for the study. If we see that x amount of people have more than x amount of something, we will suspend the study even if they're not adverse events. At the time of renewal we have to tell the IRB. If everyone dropped out, we have to say we have several people and explain those reasons.

Follow-up 19 - RML: Is that relatively new?

(b) (6) That was in place when I came here (b) (6).

(b) (6) It's more on macro level. They want to see if we recruited 100 people and only 2 completed they would look into it, but if 5 didn't complete out of 100, the IRB would not look into it.

Follow-up 20 - (b) (6), (b) (5)

[redacted]

Follow-up 21 - RML: I think with some adverse events, it's hard to tell when they were submitted. I see the certified date. Was it the date submitted or the date that IRB certified receiving the document. It wasn't clear whether certified date was IRB's or EPAs.

(b) (6) I can't tell you now it's computerized so now its easier to tell. We

will look into it.

Follow-up 22 - CD: (b) (6), (b) (5) [redacted]

[redacted]

17. **If a subject experienced symptoms that were clinically significant enough to require an exposure session to be stopped, why are those instances not considered adverse events or unanticipated problems?**

(b) (6) There were 3 individuals, from the studies, where the exposure was stopped -- (b) (6) [redacted] reports were filed. (b) (6) we can go through that, but (b) (6) wrote a letter explaining why an adverse event report wasn't filed. We believed it was unanticipated or unconnected to the study. We're unclear to what that question means.

Two of the incidents were reported, and the third was reported later on. The reason why is provided in the letter you from (b) (6) . One of the incidents involved a benign atopic tachycardia. It was unlikely the event was related to the subject's participation in research. It was observed in both clean air and PM exposure, and we do not think it was

study related. The IRB told us that we were right, and technically we did not have to submit it. If you entered it into the system, it'll spit it out anyway and say you don't have to report. However, we have so few adverse events when compared to what you might see in typical studies. Some HSR studies have several adverse events a day or several per week. (b) (6) said that we should just put all of our incidents in anyway – we are erring on the side of caution.(b) (5)

Follow-up 23 - AM: There were some instances with DEPOZ subjects that the session wasn't stopped in the middle. The subject was not allowed to participate in one of more sessions. We're asking what events lead to not participating in the study.

(b) (6) One has to understand that there is safety and there is science. Safety is a primary concern, but it is not the only concern. Some people are eliminated for science reasons as well. For example, a few of the DEPOZ subjects had a decrease in lung function. That's what happens with ozone. There's a certain amount of people that are poor responders. Some people when exposed to ozone have a large decrement in lung function and others have a small decrement -- this is a consistent feature. Individuals who are poor responders will have a larger decrement during the second day of exposure to ozone. There is no way to predict who is a poor responder. Our research is focused on the basis of susceptibility and who is a good responder and who is a poor responder. We know that when exposed to ozone on day 1 and exposed to ozone on day 2, your day 2 lung function will be less than day 1. On days 4-5-6 it's even less. In the terms of DEPOZ, we know that if someone is exposed and has a 5% drop in lung function, the subject's lung function will decrease even more on the next exposure day. When these people were exposed, they had a significant drop in lung function, which is completely normal. We knew they would have a lung function drop that was greater than this on the second exposure day. We decided not to expose them the next day.

(Reviewer's Note: See Source 6: Follinsbee study. The study's executive summary actually states that the lung function decreases further on day 2 and day 3 exposures to ozone but returns to close to normal on days 4 and 5 of ozone exposure.)

Follow-up 24 - AM: But some of these folks were brought back for later exposures?

(b) (6) Right, but not for back to back ozone exposures. Clean air then ozone the next day, that's fine. They would not be called back for back to back ozone because we know their lung function is light in the first one, and we don't want a drop in lung function too low. It's measuring on the side of caution. If you look at previous studies from other HSR organizations -- they exposed them. It's just our decision that it drops some data points and we don't want to incur that risk. If you want the paper that shows the drop in repeated exposure of lung function we'll be happy to send that.

(b) (6) This concept of responder and non-responder is very clear with ozone from a cardiovascular point of view. The rhythm of filtered air and unfiltered air part is a benign rhythm. For (b) (6) the rhythm the individual had was a safe rhythm and won't become life threatening. It's rare to sustain after a few beats. This is not a clinical worry to the individuals. As (b) (6) was saying, it's more of scientific integrity more than a health thing. The other aspect of that particular case, as a cardiologist, how do we make a diagnosis of heart issues? We put a holter monitor on the individual to learn more – to determine whether they have irregular heart beats. This is very common in people with older age. It's a nuisance and won't bother you. You can put them on a beta blocker and that will generally suppress arrhythmias. In this part case, the subject when asked during the screening if (b) (6) had palpations, (b) (6) said no. When we talked to (b) (6) about the rhythm, (b) (6) said this is what I have at home. We know why (b) (6) has palpitations. Our recommendation to (b) (6) was to tell doctor about the palpitations.

Follow-up 25 - TW: Is this pre-ventricular contractions (PVC)?

(b) (6) PVC relates to an early beat that arises in the ventricle. Premature beats are benign, whether they occur in the atria or ventricle. We don't study people who have ventricular abnormalities, dilated hearts, or have arrhythmias. I wouldn't classify PVC or a premature atrial beat as a serious problem unless we know the heart it is occurring in.

(b) (6) (b) (6) has these palpations at home. The definition of what's reportable is something related to study or something that is unanticipated. This doesn't fit either of those and isn't related to study. Also, we didn't write it in the letter, but if (b) (6) told us it wouldn't have been unanticipated. The reality was it was unrelated to the study.

(b) (6) We are guided by the definition of adverse event's in the Institute of Cancer. We gave you that link. This is something that occurs through the whole field. Adverse event decision are made by individuals and sometimes they are open to interpretations. We desire to err on the side of caution. You'll see (b) (6) who input lots of adverse events. Even for someone who comes in and has a cold. (b) (6) would have put that in and the computer would spit it back to (b) (6) and other researchers would think ahh that incident is not related to the study and won't input it. We don't have 10 a week.

In that regard, we would like to discuss the following study subjects exposures sessions:

(b) (6): **[ANALYST NOTE: I think this was the (b) (6) that was disqualified because of the heart trouble.]**

(b) (6)

RML: We created a table for the medical records. I know the person was encouraged to drink food and water. **[ANALYST NOTE: RML read aloud information from the patient's health record. PII was**

protected.] I'm trying to figure out whether it was stopped or may have been one who skipped a session.

(b) (6) For clarification, ozone causes people to cough and that's written in the consent form. It's short term and resolves quickly (same day or even in minutes or hours), rarely does it persist for a day, but not usually longer after that.

Follow-up 26 - RML: I know (b) (6) moved away, but there was something noted about a skipped session. We can get back with you if we have questions.

(b) (6) [redacted]

(b) (6) [redacted]

(b) (6) [redacted]

(b) (6) You do have to make an effort and has to be coordinated.

(b) (6) So we had to disqualify (b) (6) because (b) (6) couldn't do it.

(b) (6) [redacted]

(b) (6) A participant can quit at any point of the study, they can just say I don't want to do this. This person exercised that right and didn't want

to do it, so it was stopped.

Follow-up 27 - RML: Our concern was chest tightness with deep inspiration. At what point does this raise a red flag?

(b) (6) Remember we do a pulmonary function test when they come in, so we have absolute, not subject values and are clinically evaluated by nurses and physicians to make sure nothing is wrong. That's why we have a follow up day.

RML: But you're not showing there's issues with the procedure. It's the pulmonary function test?

(b) (6) Chest tightness and inability to take a deep breath is expected with ozone. It's usually fixed with taking a narcotic. It's a neurologically-mediated symptom and can be stopped.

Follow-up 28 - KG: You would say that even individuals with heart palpitations are healthy?

(b) (6) yes.

Follow-up 29 - KG: One follow up that deals with OMEGACON. One subject had holter and experienced an arrhythmic event and subject was still placed in chamber. Is that normal procedure or was the arrhythmia missed?

(b) (6) If you tell me the # of this patient, I can follow up. The way the holter is done it's not there for safety. It's interpreted after or during the study. It's not a safety endpoint. The safety endpoints are more about what we do in here. (b) (6) have talked about the value of the holter beforehand. It's not an effective tool to detect arrhythmias.

(b) (6) It was done in previous studies but is not effective and was discontinued. It's not very cost effective. Monitoring rhythm for safety

purposes is to monitor the telemetry in real time with computer analysis with alarms that go off if there is an abnormal rhythm.

(b) (6) You take your car to the mechanic and say when I drive my car there is a weird noise somewhere. The mechanic says reproduce it, but I can't. It's possible something showed on the holter when we got it and analyzed it and isn't a reproducible incident that you see consistently and that telemetry picks up.

(b) (6) we pay attention to the holter because we require a steady rhythm. Other individuals that aren't interested in those endpoints (blood pressure and pulse) they will not pay attention to those at all because they don't increase an individuals risk.

(b) (6), esteemed researchers never used a holter on subjects or any other cardiac monitoring.

(b) (6) Give us the number of the individual and we'll look it up for you.

RML thanked everyone. She told them we'd meet again in June to discuss early findings.

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Administration Workpaper

Prepared by Alicia Mariscal 12/12/2012

Assignment: 2013 - 3540 - OPE-FY13-0001 - Evaluation of EPA's Human Subjects Research
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Goal: Sound Science - Improved Understanding of Envionmental Risks - and Greater Innovation to Address Environmental Problems
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Assignment Guide Name: Auditee Communication Workpapers

Origination Doclink:
Subject: R1 - NHEERL Follow-Up Conversation 06/20/13 **Subsection:** 07

Created by Alicia Mariscal on 07/02/13

Reviewed by: Renee McGhee-Lenart, 7/09/13, workpaper is satisfactory.

Date: June 20, 2013

Location: Teleconference between OIG staff in Kansas City and Washington DC and NHEERL staff in Chapel Hill, NC.

Purpose: To discuss several follow-up questions related to human subjects (b) (6) [redacted]

Teleconference Participants:
EPA NHEERL, EPHD:

(b) (6) [redacted]

(b) (6) [redacted]

OIG:
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Sources:

1. 06/19/13 emails between NHEERL and Alicia Mariscal regarding study subject (b) (6) electrocardiograms (ECGs) from 2009 and 2010:

1a. 06/19/13 emails: **RE_ Questions Re_ ECG with attachment.pdf**

1b. (b) (6) ECG from 05/2009: **05-2009 (b) (6) ECG Redacted.pdf** (The subject mailed our team a hardcopy version of this ECG report. This document has been secured in Alicia Mariscal's workspace in the EPA OIG Washington, DC office.)

1c. In one of the emails under **1a.** above, NHEERL sent our team (b) (6) s ECG report from 08/22/2007 and a letter from Triangle Family Practice on 08/31/2010: **(b) (6) Redacted.pdf**

2. 06/20/13 email from Alicia Mariscal to NHEERL staff requesting documentation for (b) (6):

06-20-13 Documentation Request Re_ Two Subjects.pdf

3. On 06/25/13 our team received the hardcopy documents totalling 3 pages (requested under **2a.** above). These documents have been secured in Alicia Mariscal's workspace in the EPA OIG Washington, DC office:

3a. (b) (6) Bronchoscopy Procedures Flow Sheet from 04/20/11

3b. (b) (6) 08/23/2007 cardiological review of (b) (6) 08/22/2007 ECG

3c. (b) (6) 08/22/2007 ECG report.

4. WP F.19.e.9: Subject (b) (6) Interview

5. WP B.07.b.1: 5th Edition - NHEERL Guidance, see Attachment #1

6. National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP), "CTEP, NCI Guidelines: Adverse Event Reporting Requirements," January 1, 2005 (Accessed online at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/newadverse_2006.pdf by Alicia on 07/01/13):

NCI AE Reporting Requirements 01-01-2005.pdf

7. (b) (6) Adverse Event Report to the IRB for event dated 04/27/2011:

UPAE_09-1344_2577_May2011_(b) (6) .pdf

Scope: To ask NHEERL follow-up questions related to human subjects (b) (6) regarding issues such as health considerations reviewed prior to accepting a subject into a study, IRB report filing timeframes and the number of working days that NHEERL took to file 2 adverse event reports with the IRB, as well as one subject's experience of decreased oxygen saturation during a bronchoscopy.

Conclusion:

No conclusions are drawn in this workpaper. However, the information in this workpaper will be incorporated in other workpaper steps as needed.

Interview Details:

[ANALYST NOTE: The text below represents selected excerpts and summaries, mostly paraphrased, of our conversation with (b) (6) .]

REGARDING (b) (6) & (b) (6) :

Alicia clarified that we were speaking about (b) (6) who then later wanted to participate in DEPOZ (as (b) (6)) and not LAMARCK. (Source 1a., p. 1, top to middle of page where (b) (6) referred to (b) (6) (1st sentence), (b) (6) (first sentence in 2nd & 3rd paragraph) and LAMARCK (1st sentence of 3rd paragraph))

(b) (6) confirmed that we were indeed speaking about (b) (6)

Alicia: How was what happened to (b) (6) that resulted in the subject being dismissed from the study different than what was happening to the same subject when (b) (6) ?

(b) (6) . One of the endpoints for the DEPOZ study is the holter monitor report; scientifically, we cannot use the data.

(b) (6) DEPOZ was an exercise study, and there was a slight difference there. During DEPOZ the subject was exposed to ozone, and then on the follow-up day the ventricular ectopic beats were

noticed.

(b) (6) The ectopic beats may occur during exercise, and we didn't see it during the training day. It could have something to do with it.

Renee: In OMC, the subject looked (b) (6) .

(b) (6) When we got the first trace in August 2007, for the PILOT study, that is when we took the most pause. We thought about it and sent it to our cardiologist, who was (b) (6) at the time (and (b) (6) was under contract with NHEERL). Given that they had no history and no symptoms, then it was unlikely that a heart attack was the cause. The electrodes could've been placed in the wrong place. "Abnormal" just means not in the normal range, or not in the average range.

(b) (5), (b) (6)

(b) (6), (b) (5)

(b) (6), (b) (5)

(b) (6) Study-specific information is in the subject's file under a specific study. However, the initial physical the subjects get is kept in their medical chart that is not study specific, or filed that way.

Alicia: So this information, including the repeat physical, would be in (b) (6) general medical chart?

(b) (6) Yes. The subjects come in for a physical, but if it has been more than a year, we do a repeat physical. The ECG that you sent us by email (Source 1b) was (b) (6) repeat physical.

(b) (6) And the repeat physical is based on what happened to the subject over the past year. (b) (6) would've focused on asking (b) (6) all about having any symptoms or any changes in (b) (6) heart condition since the last physical took place.

Alicia gave some of the context about what the subject told us during our interview with (b) (6) and how the subject didn't seem to have an understanding of what "ventricular ectopic beats" meant. (Source 4, responses to Question 16, items h., n.; also, Answer to Follow-Up Question #12 and Auditor Dunlap note just below that)

(b) (6), (b) (5)

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Renee: When (b) (6) was asked to no longer participate in the DEPOZ study, (b) (6) was told to follow-up with (b) (6) doctor?

(b) (6) can speak to you about DEPOZ better than I. In of itself (b) (6) condition was completely benign, but if over time it altered its characteristics, it could put (b) (6) at risk for future cardiac events. In isolation, ectopic beats are not an issue, but if it became more and more sustained, if it didn't go away and (b) (6) kept having ectopic beats, that is an indicator for being a higher risk in the future. That's why (b) (6) advised to go and see (b) (6) physician. (b) (6)

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REGARDING (b) (6) :

Alicia: For study subject (b) (6), where the subject experienced tachycardia while exposed to air pollution particles and then was later hospitalized overnight, was this a "serious" and "unanticipated" event as defined by the NHEERL Guidance? (Source 5, Attachment 1, p. 38, sections 8.1.2 and 8.1.3)

(b) (6) We use National Cancer Institute's (NCI) guidelines for how we classify adverse events, and what happened with (b) (6) is nowhere near serious. (Source 6, p. 7 for definitions of AE

and SAE) It was a mild event. We don't have to say whether it is serious. It is nowhere close to being a SAE (Serious Adverse Event), which is prolonged and involves prolonged hospitalization.

Renee: (b) (6), (b) (5)

[redacted]

(b) (6) (b) (6), (b) (5)

[redacted]

(b) (6) IRB also goes by the NCI Guidelines.

(b) (6) (b) (6), (b) (5)

[redacted]

The guidance is supposed to be updated by the HRPO (Human Research Protocol Office, referring to the Director), and as of 2010, it is due for upgrade.

Alicia: To clarify, NHEERL classifies what happened to (b) (6) as an adverse event that is not serious and is unanticipated?

(b) (6) Yes, we consider what happened to (b) (6) to be an AE (Adverse Event) and unanticipated. Whether it is an AE or SAE, that decision is made by the HRPO. The HRPO wrote the guidelines and would've assigned the definition. So if the HRPO felt it was an SAE they would've said so.

(b) (6) Also, the IRB would push back if they disagreed/thought that the HRPO offered an inaccurate classification of an event.

Renee: The IRB form does have a section for whether it was anticipated or not, but no section for whether it was serious…

(b) (6) The IRB makes its own determination about seriousness, and for NHEERL the HRPO makes that determination.

Renee: Then that is really the basis of the timeliness of how you report?

(b) (6) Yes, NHEERL makes a determination about the seriousness or not of an AE, but the final determination is made by the IRB.

(b) (6) You bring up a very good point. The difference between UP (Unanticipated Problem) and AE affects how quickly we report to the IRB, and we report as immediately as possible. With the exception of that one XCon (b) (6)) that you may talk about. We report very quickly. Hopefully that clarifies a little bit.

Renee: For this (b) (6) it was reported in three working days. If you consider it not serious but unanticipated, then NHEERL would have up to 10 working days to report it to the IRB.

REGARDING (b) (6) :

Alicia: Next we'd like to speak to you about study subject (b) (6) , who experienced a persistent cough after being exposed to ozone.

(b) (6) To clarify, the subject did not develop a cough after being exposed to ozone, but rather developed a cough sometime between the last exposure and the subject's next visit to the lab three weeks later. I would really urge you not to see it as "after an exposure" but instead "after an exposure, but not present after 48 hours after an exposure." The subject came in and had an exposure to diesel and ozone. The subject had a physical on 11/1/10, was cleared and had no cough. February 16th was Day 1 of Exposure #1, and it was a 2-hour combination exposure of diesel and ozone. Afterwards the subject had no cough beyond the short-term cough that we commonly see. On February 17th, the subject had a shortened diesel exposure due to a fire alarm. **On February 18, the subject came in for a follow-up and did NOT have a cough. The subject was NOT exposed on February 18th.** On March 9, (b) (6) comes in and is fine. During pre-exposure (b) (6) does a pulmonary function test, and because (b) (6) is exerting (b) (6) (b) (6) starts coughing. On March 9th, because the subject had a cough before any exposure "we broke the code". (Alicia asked and (b) (6) explained that in a double-blind study, the investigators didn't know what they were exposing the subject to, so they broke that code and found out that the subject was going to be exposed to clean air that day.) The subject was also evaluated by (b) (6) who determined that if the exposure was going to be a PM (particulate matter) exposure we wouldn't have continued, but since it was going to be clean air, that can only be good for you, and decided that the subject was going to be exposed to the clean air that day. At that time the subject now claims that (b) (6) had a cough, but we thought it was only upon exertion. (b) (6) started coughing in the chamber, and 48 minutes in we stopped the exposure. **On March 9th the**

subject was not exposed to particles or pollutants but was exposed to clean air.

At this point during (b) (6) summary Alicia and Renee stopped (b) (6) and attempt to clarify that the description of these dates and exposures do not match what was stated on the IRB report. (Source 7, pgs. 1-2) Alicia and Renee explained that the IRB report states that **"On 2/18, [redacted] was exposed to ozone alone" and "On 3/9, [redacted] returned for [redacted] second arm of the study. [redacted] came presenting a cough and was not exposed."** (Source 7, bottom of page 1 to top of page 2)

(b) (6) "(b) (5) [redacted]

(b) (6) [redacted] thank us for pointing out the discrepancies in the dates between their records and what was stated on the IRB report. They had not been aware of the dates stated on the IRB report.

(b) (6) (b) (6), (b) (5) [redacted]

Renee: (b) (6) [redacted] But, what happened where what was happening to this subject would not be considered an AE until April?

(b) (6) (b) (5) [redacted]

Renee: The subject had a cough, that was or not research related, and then the subject came back in April and the cough was still lingering, and because NHEERL was not sure if it was connected to the research or not at that point, it was reported to the IRB?

(b) (6) Yes, and subject said had treated (b) (6) with echinacea, and had vomited. (b) (6) examined the subject and gave [redacted] medication. And, because the cough was temporally related to the study they submitted a report to the IRB.

Renee: So it would fall under a not serious but unanticipated (due to the prolonged cough) event?

(b) (6), (b) (5) [redacted], but said yes, it was a not serious but unanticipated event.

Renee: We're asking because the IRB report was turned in a little bit late, on the 11th or 12th working day.

REGARDING (b) (6) [redacted]

Alicia stepped away from the conversation for a few minutes while Renee asked (b) (6) [redacted]

about (b) (6) who was discontinued from the study due to decreased oxygen saturation.

(b) (6), (b) (5)

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Renee: Decreased oxygen saturation by itself wouldn't be considered an AE?

(b) (6), (b) (5)

(b) (6), (b) (5)

Renee asked if she could request any additional info about this subject. (As noted in Source 2, p. 1, item a., after this conversation we requested this subject's Bronchoscopy Flow Sheet that would note the lowest level of oxygen saturation the subject reached during this bronchoscopy. See Source 3a. which notes on page 1, item 14., that on 04/20/11 the subject's saturation decreased to 84% post bronchoscopy) (b) (6) requested that they copy both (b) (6) in case (b) (6) is out of the office. (b) (6) also asked about when the draft report may be expected.

Renee: (b) (5)

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We thanked them for their time, and the meeting ended.

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